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SYMPOSIUM ON 'GENETICS AND NUTRITION'

Genetic differences in metabolism of farm animals

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Within a species any observed differences in metabolism may be due to genetic effects, to environmental influences or to both these factors. The first step in any attempt to breed for improvement is to identify and separate these factors as far as possible. Differences due solely to environment can be recognized because they are altered by changing the environment. Genetic differences on the other hand are fixed characters which are handed on from one generation to the next. If inheritance accounts for most of any observed variation, offspring will resemble their parents; if the variation is due to environmental factors then offspring should no more resemble their parents than do unrelated animals. Estimates of heritability are usually based on such comparisons. Often both inheritance and environment interact to produce the observable character, and generally speaking the broader the trait under investigation the more difficult will it be to separate these effects and the more complex the genetic control is likely to be.

In man, genetic differences in metabolism can be exemplified by any number of inborn errors of metabolism (Brock & Mayo, 1972). Many of these heritable disorders are the result of single gene mutations which produce readily recognizable clinical symptoms in the affected individual. Although many have been described, they are in fact mostly rare conditions but have received considerable attention not only because of their medical implications but also because they provide useful model systems for comparative studies of enzyme function at a molecular level. It is much more difficult to find similar examples in farm animals. This is probably due to the fact that the animal breeder selects against any obviously deleterious condition and also because farm animals are in general not subjected to the rigorous health screening procedures applied to man. The objective of this paper is to show that genetic differences in metabolism certainly exist in farm animals even though they may not produce clinically manifest disorders.

Table 1. *Enzymes and other proteins which show genetic polymorphism in sheep red cells. (Single gene effects)*

(Variants which are known to interrelate phenotypically are linked by brackets)

Variant	No. of genes	Manifestation	Reference
Na-K activated ATPase	2	High and low K	Agar, Evans & Roberts (1972)
Nucleoside phosphorylase	2	Deficiency	Tucker & Young (1976)
Arginase	(2?)	Deficiency	Unpublished
Amino acid transport	2	GSH deficiency Amino acid accumulation Low Na+K	Young, Ellory & Tucker (1976)
Carbonic anhydrase	2	Electrophoretic difference	Tucker (1975)
γ-glutamyl cysteine synthetase	2	GSH deficiency	Young & Nimmo (1975)
NADH-diaphorase	2	Electrophoretic difference	Brewer, Eaton, Knutsen & Beck (1967)
'X'-protein	2	Deficiency	Tucker (1975)
Inosine permeability	2	Impaired uptake	Young (1976)
Haemoglobin	2	Electrophoretic difference O_2-affinity Structural difference	Agar, Evans & Roberts (1972)
Red cell antigens	Many	Serological tests	Tucker (1975)

Some idea of the complexity of the genetic control underlying metabolic processes in the whole organism can be gained by studying enzyme variation at a cellular level. The genetic differences in the red blood cell provide a good example of this complexity. The metabolic processes in this cell are directed towards its chief function of transporting oxygen and carbon dioxide about the body. Table 1 lists the red cell enzymes and other proteins which are known to show polymorphism in the sheep. They all arise as a result of single gene mutations and as such are easily measured and separated from environmental factors. Most of these variants occur quite commonly so that any particular sheep can possess a great number of variants all of which contribute to the net metabolism of its red cells. Moreoever a variation at one locus can influence the expression of a character controlled at another locus. Thus, a genetic defect in amino acid transport (Tr locus) results in a deficiency of reduced glutathione (GSH), an abnormal accumulation of certain amino acids and a corresponding drop in the concentration of sodium and postassium in the cell (Young, Ellory & Tucker, 1976). Red cell Na and K concentrations are also under the control of genes at another locus (Ke or M locus) which define the presence or absence of a certain blood group antigen which affects active transport of K across the membrane (see Tucker, 1975).

Since most of these variants, even the deficiencies, do not give rise to any clinical disorder it could be argued that they play no major role in the metabolism of the mature red cell and are therefore of no practical significance. On the other hand, some explanation has to be put forward for the maintenance of the wide range of these and other polymorphisms that exist in all species. It seems probable that such variants do contribute to the balanced mechanism which evolves in an animal

species in response to its environment. Heterosis or heterozygote advantage is a well established principle. The sheep red cell has been used here as an example; similar enzyme variations in horse, cattle, pig, goat or chicken red cells could have been cited (see McDermid, Agar & Chai, 1975).

The red cell GSH deficiency which is particularly prevalent in the Finnish Landrace breed of sheep provides an example of a single gene effect which probably is detrimental to the individual. Such red cells have a life span which is at least 40 d shorter than normal (Tucker, 1974) and there is evidence that sheep with this deficiency may be prone to anaemia. Since the chief function of GSH is to protect the cell against oxidative damage, it might be expected that GSH deficient cells (Low GSH) would not be able to withstand oxidative stress as well as normal red cells (High GSH). This was found to be the case in sheep fed on kale which is known to possess a toxic agent. Low GSH sheep became more anaemic than High GSH sheep and their red cells contained more Heinz bodies (Tucker & Kilgour, 1973). Heinz bodies are denaturated haemoglobin which precipitates in the cell when haemoglobin undergoes oxidative destruction. It was found in fact that even under conditions of normal grass feeding Low GSH red cells contained a higher percentage of Heinz bodies than High GSH cells.

The red cell Na and K polymorphism found in sheep (see Agar, Evans & Roberts, 1972), goats (Rasmusen & Hall, 1966) and cattle (Ellory & Tucker, 1970) provides an example of how small genetic effects may be superimposed on major genetic differences so that the final phenotypic value measured represents the sum effect of several gene influences. If blood Na and K concentrations are measured in practically any breed of sheep, a discontinuous, bimodal distribution is found. Some sheep have red cells with low Na and high K (HK type) and some have cells with high Na and low K (LK type). This difference is controlled by an allelic pair of genes, the gene for LK being dominant to that for HK. However, within these two major classes, minor differences can be detected which are probably also under genetic control. Thus red cell K levels can be influenced by sex, female sheep of both HK and LK type having higher mean values than male sheep (Rasmusen & Hall, 1966). Also, as mentioned previously, LK or HK sheep red cells which have an amino acid transport defect have lower Na+K concentrations than normal. Within the HK and LK classes there are marked breed differences, and plasma K concentrations also may be influenced by breed (Taneja, Narayan & Ghosh, 1969; Eagleton, Hall & Russell, 1970).

In farm animals many studies have been undertaken to seek correlations between blood marker genes and factors of economic importance, but mostly they have been disappointing. This is perhaps not too surprising, for most growth and production traits are influenced by many aspects of the animal's physiology and it follows therefore that most inherited characters of economic importance are the net result of the activity of genes at a large number of loci. A few potentially important correlations have been reported, such as those between transferrin types and fertility in sheep and cattle or between amylases and milk yield in cattle or haemoglobin type and fertility in sheep (see Spooner, 1974). Recent work has

brought to light an interesting association between the H blood group system, meat colour and body length, the porcine stress syndrome and haemorrhagic diathesis in pigs (Rasmusen & Christian, 1976; Agergaard & Nielsen, 1976; Rasmusen, 1976). These studies and current investigations of associations between blood types and disease resistance give hope that in the future more significant findings may be reported.

In discussing genetic variation in the whole organism, recent work on mineral metabolism should be considered. It has been shown that some sheep breeds are more susceptible than others to copper deficiency and there are clear-cut breed differences in the incidence of swayback and copper poisoning (see Weiner, 1971). In both cattle and sheep different breeds given the same diet and kept together under the same conditions will typically have different concentrations of a number of minerals, including calcium, phosphorus and magnesium, in their blood. Breed differences in the incidence of milk fever and grass tetany in cattle and an inherited factor in the incidence of a goitrous condition in lambs have also been reported (Weiner, 1971).

In the field of mineral metabolism more research into fundamental biochemistry might be rewarding; for example, selenium, which is an integral component of the glutathione peroxidase molecule, is thought to be involved in the aetiology of white muscle disease in ruminants and of liver necrosis in pigs. Now the glutathione peroxidase molecule in situ is unsaturated in respect of Se, and moderate increases of Se in the diet have been shown to stimulate markedly the activity of this enzyme in the red cell (Thompson, McMurray & Blanchflower, 1976). Since peroxidase is intimately involved in the protection of the cell against oxidative damage, any induced activity of this order may be beneficial to the animal, particularly where the protective mechanisms may not be functioning maximally, for example in GSH deficiency. At the moment this is speculation but it illustrates the way in which a combined biochemical and genetical approach might lead to a better understanding of metabolic processes.

In conclusion, investigations at a cellular level reveal that there must be a great diversity of genetic factors controlling metabolism. There are few examples of single gene effects which result in clinically recognizable metabolic disorders and most of the problems encountered in farm animal husbandry are probably the result of diverse influences. The over-all metabolism of an animal is the sum total of many genetically controlled processes which are in a state of balance, a balance which may well be affected by changes in environment. Many metabolic diseases are caused simply by nutritional excesses or deficiencies, and can be corrected by controlled feeding. This is the rationale behind the Compton metabolic profile tests (Payne, 1972). The tests deal with environmental causes of variation; they serve to highlight major changes in nutritional states, and as such are useful. The genetic influences are more subtle and are difficult to analyse and define precisely. However, as we learn more about the biochemical genetics both of individual cells and of the whole organism we can begin to hope that in the future it may be possible to introduce genetic considerations into schemes for providing the correct

nutritional requirements for farm animals or the correct animals for a particular environment.

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